IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Ohlmeyer et al.	*Confirmation No.:*	2697
Serial No.:	10/046,616	*Group Art Unit:*	1624
Filed:	01/14/2002	*Examiner:*	Balasubramanian, Venkataraman
Title:	BRADYKININ B_1 RECEPTOR ANTAGONISTS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AFFIDAVIT UNDER 37 C.F.R. §1.132

Dear Sir:

I, Maria L. Webb, hereby state and declare that:

1. I am a citizen of the United States of America and a resident of Flemington, New Jersey;

2. I earned a B.A. in Biology from Montclair State College in Montclair, New Jersey, in 1977, an M.S. degree in Physiology from The Pennsylvania State University in University Park, Pennsylvania, in 1980, and a Ph.D. degree in Physiology from The Pennsylvania State University in University Park, Pennsylvania, in 1983. My primary area of research, both academic and industrial has been in the areas of physiology and molecular pharmacology. I am presently Vice President of Drug Discovery at Pharmacopeia Inc., in Princeton, New Jersey. Prior to my employment at Pharmacopeia, I was a Principal Scientist in Cardiovascular Biochemistry & Drug Discovery at Bristol-Myers Squibb Corp. in Princeton, New Jersey, and a Research Assistant Professor in Department of Pharmacology at The Pennsylvania State University College of Medicine in Hershey, Pennsylvania;

3. I am a member of the American Association for the Advancement of Science, American Society of Pharmacology and Experimental Therapeutics, American Chemistry Society, and Society of Biomolecular Screening;

4. I am the author of 71 papers in the area of pharmacology, including one published paper[1] (Exhibit A) and one paper in preparation[2] on the subject of Bradykinin B1 receptor and its role as a therapeutic target;

5. I have reviewed and do understand the contents of the above-identified application, which is directed to antagonists of Bradykinin B1 receptor and their methods of use. I have also reviewed the Office Action in the present case, Serial Number 10/046,616, dated December 3, 2003.

6. As a person of skill in the art, I would accept the disclosures of the results *in vitro* presented in the application as predictive of utility for treatment of inflammation (including inflammation associated with edema, rhinitis, septic shock, multiple sclerosis, atherosclerosis, Alzheimer's disease, and closed head trauma), pain (including pain associated with inflammation, chronic pain, and dental pain), hyperalgesia, post-capillary resistance, diabetic symptoms associated with insulitis (such as hyperglycemia, diuresis, proteinuria, and increased nitrile and kallikrein urinary tract excretion), and edema.

7. Furthermore, as a person of skill in the art, I declare that it would have been within the ordinary skill in the art to generate pharmaceutical dosages of the Bradykinin B1 receptor antagonists disclosed in the present application to be used in

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[1] Horlick, R.A., Ohlmeyer, M.H., Stroke, I.L., Strohl, B., Pan, G., Schilling, A.E., Paradkar, V., Quintero, J.G., You, M., Riviello, C., Thorn, M.B., Damaj, B., Fitzpatrick, V.D., Dolle, R.E., Webb, M.L., Baldwin, J.J., and Sigal, N.S. Small molecule antagonists of the bradykinin B1 receptor. *Immunopharmacology,* 43:169-177 (1999).

[2] Deblois, D., M. Sherman, M. Ohlmeyer, V. Paradkar, B. Strohl, and Webb, M.L. Development of a bradykinin B1 model of hyperalgesia in the primate. (in preparation for *J. Pharmacol. Expt. Ther.*)

methods of treatment of the above-mentioned disorders. Such dosing could be done as a matter of routine and without undue experimentation.

8. At the time prior to July 15, 1999 priority date of this application, it was widely accepted in the art that Bradykinin B1 receptor antagonists are useful in treatment of various disorders characterized by symptoms of inflammation and pain. A number of early references support this view. For example, a 1994 publication by Menke et al.[3] (Exhibit B) stated that Bradykinin B1 receptor is implicated in chronic inflammation and hyperalgesia (increased sensitivity to pain or enhanced intensity of pain sensation). In a 1997 publication, Rupniak et al.[4] (Exhibit C) gave further support to the understanding that Bradykinin B1 receptor antagonists may be clinically useful as anti-inflammatory and analgesic drugs. Also in 1997, Rang et al.[5] (Exhibit D) summarized the known role of Bradykinin B1 receptor antagonists in treatment of inflammation, pain, and hyperalgesia. In another 1997 paper, Stewart et al.[6] (Exhibit E) reviewed known Bradykinin B1 receptor antagonists which were found to be useful in treatment of hyperalgesia, edema, inflammation, and closed head trauma. Finally, a March 1999 publication by Ahluwalia et al.[7] (Exhibit F) discussed the role of Bradykinin B1 receptor antagonists in treatment of edema, pain, inflammation, and shock.

9. Moreover, later published references confirmed the anti-inflammatory and anesthetic role of Bradykinin B1 receptor antagonists. In one key publication, Pesquero et al.[8] (Exhibit G) demonstrated that Bradykinin B1 receptor knockout mice were healthy and exhibited hypoalgesia (decreased sensitivity to pain) and diminished inflammatory

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[3] Menke et al., Expression Cloning of a Human B1 Bradykinin Receptor, *The Journal of Biological Chemistry*, 269(34):21583-21586 (1994).

[4] Rupnial et al., Effects of the bradykinin B1 receptor antagonist des-Arg^9[Leu^8]bradykinin and genetic disruption of the B2 receptor on nociception in rats and mice, *Pain*, 71:89-97 (1997).

[5] Rang, H.P. and Perkins, M.N., The Role of B1 and B2 Bradykinin Receptors in Inflammatory Pain, *Molecular Neurobiology of Pain*, Progress in Pain Research and Management, Vol. 9 IASP Press (1997).

[6] Stewart, J.M., Gera, L., Chan, D.C., Whalley, E.T., Hanson, W.L. and Zuzack, J.S., Potent, long-acting bradykinin antagonists for a wide range of applications, *Can. J. Physiol. Pharmacol.* 75: 719-724 (1997).

[7] Ahluwalia, A. and Perretti, M., B1 receptors as a new inflammatory target (Could this B the 1?), *TiPS*, 20:100-104 (March 1999).

[8] Pesquero, J.B., Araujo, R.C., Heppenstall, P.A., Stucky, C.L., Silva, J.A., Walther, T., Oliveira, S.M., Pesquero, J.L., Paiva, A.C.M., Calixto, J.B., Lewin, G.R., and Bader, M., Hypoalgesia and altered inflammatory responses in mice lacking kinin B1 receptors, *PNAS*, 97(14):8140-8145 (2000).

responses. In this mouse knockout model, the function of the Bradykinin B1 receptor is shut down and, therefore, it is very similar to what one would expect from the administration of a Bradykinin B1 receptor antagonist. This study demonstrated that Bradykinin B1 receptor antagonists would be beneficial in treatment of inflammation and pain and are expected to have minimal side effects. In addition, Rupniak et al.[9] (Exhibit H) summarized expected benefits of Bradykinin B1 receptor antagonists in treatment of pain and inflammation. Bock et al.[10] (Exhibit I) discussed potential role of small molecule Bradykinin B1 receptor antagonists in treatment of inflammation, pain, asthma, multiple sclerosis, and cancer. Bedos et al.[11] (Exhibit J) discussed role of known Bradykinin B1 receptor antagonists in treatment of inflammation and pain. Ferreira et al.[12] (Exhibit K) reported utility of Bradykinin B1 receptor antagonists in treatment of pain and hyperalgesia. Ni et al.[13] (Exhibit L) discussed potential use of Bradykinin B1 receptor antagonists in treatment of edema, inflammation, toxic shock, pain, and hyperalgesia. Finally, Wood et. al.[14] (Exhibit M) described effects of small molecule non-peptidic Bradykinin B1 receptor antagonists in treatment of pain, inflammation, and hyperalgesia. It should be noted that the compounds disclosed in the present application are also small molecule non-peptidic Bradykinin B1 receptor antagonists.

10. In addition, a 1998 publication of PCT application WO 98/07746 (Exhibit N) presented *in vivo* data supporting the role of Bradykinin B1 receptor antagonists in treatment of diabetic vasculopathy, post-capillary resistance, and diabetic symptoms associated with insulitis, such as hyperglycemia, diuresis, proteinuria, and increased nitrile and kallikrein urinary excretion.

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[9] Rupniak, N.M.J., Longmore, J., and Hill, R.G., Role of Bradykinin B1 and B2 Receptors in Nociception and Inflammation, Molecular Basis of Pain Inductions (Chapter 8), *Wiley-Liss, Inc.*, 149-173 (2000).
[10] Bock, M.G. and Longmore J., Bradykinin antagonists: new opportunities, *Current Opinion in Chemical Biology*, 4:401-406 (2000).
[11] Bedos et al., A Rational Approach to the Design and Synthesis of a New Bradykinin B1 Receptor Antagonist, *J. Med. Chem.*, 43:2387-2394 (2000).
[12] Ferreira et al., The Use of Kinin B1 and B2 Receptor Knockout Mice and Selective Antagonists to Characterize the Nociceptive Responses Caused by Kinins at the Spinal Level, *Neuropharmacology*, 43:1188-1197 (2002).
[13] Ni, et al., Overexpression of Kinin B1 Receptors Induces Hypertensive Response to Des-Arg^9-bradykinin and Susceptibility to Inflammation, *The Journal of Biological Chemistry*, 278(1):219-225 (2003).
[14] Wood, et al., Benzodiazepines as Potent and Selective Bradykinin B1 Antagonists, *J. Med. Chem.*, 46:1803-1806 (2003).

11. Therefore, it is my conclusion that the disclosure of the present application would enable the person of skill to treat inflammation (including inflammation associated with edema, rhinitis, septic shock, multiple sclerosis, atherosclerosis, Alzheimer's disease, and closed head trauma), pain (including pain associated with inflammation, chronic pain, and dental pain), hyperalgesia, post-capillary resistance, diabetic symptoms associated with insulitis (such as hyperglycemia, diuresis, proteinuria, and increased nitrile and kallikrein urinary tract excretion), and edema.

In testimony whereof, I hereunto set my hand and seal this 23rd day of April, 2004.

Maria L. Webb

Maria L. Webb

STATE OF New Jersey
COUNTY OF Middlesex SS:

This 23rd day of April, 2004, before me personally came the above-named Maria L. Webb, to me personally known as the individual who executed the same of his/her own free will for the purposes therein set forth.

Melanie J. Rice

Notary Public

MELANIE J. RICE
A Notary Public of New Jersey
My Commission Expires June 12, 2007